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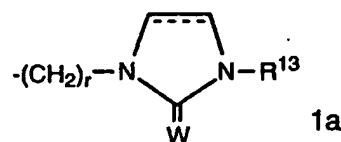
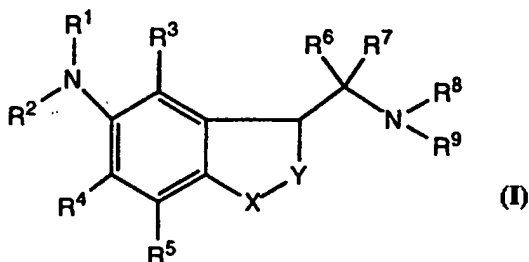
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(54) Title: AMINOMETHYLINDANS, -BENZOFURANES AND -BENZOTHIOPHENES



(57) Abstract

Compound having general formula (I) wherein one of X and Y is CH₂ and the other one is CH₂, O or S; R¹ is an aliphatic hydrocarbon group, arylalkyl, acyl, a sulphonyl group, a carbonate group or R¹¹R¹²NCO- where R¹¹ and R¹² are selected from hydrogen and a hydrocarbon group; R² is hydrogen or a hydrocarbon group; R³-R⁵ are independently selected from hydrogen, halogen, alkyl, alkoxy, alkylthio, hydroxy, alkylsulphonyl, cyano, trifluoromethyl, cycloalkyl, cycloalkylalkyl or nitro; R⁶ and R⁷ are each hydrogen or lower alkyl or they are linked together to constitute a carbocyclic ring; R⁸ and R⁹ are independently hydrogen, a hydrocarbon group or a group 1a wherein R¹³ is hydrogen, or a hydrocarbon group, W is O or S, and r is 2-6; R⁸ and R⁹ are linked together thereby forming alkylene group; have effect at central 5-HT_{1A} receptors and are useful in the treatment of psychosis, anxiety disorders, depression, impulse control disorders, alcohol abuse, aggression, ischaemic diseases, side effects induced by conventional antipsychotic agents or cardiovascular disorders.

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AMINOMETHYLINDANS, -BENZOFURANES AND -BENZOTHIOPHENES**Field of the Invention.**

- 5 The present invention relates to a novel class of substituted aminomethylindans, -2,3-dihydrobenzofuranes, -2,3-dihydrobenzothiophenes, -1,3-dihydroisobenzofuranes, and -1,3-dihydroisobenzothiophenes having effect at central 5-HT_{1A} receptors. These aminomethyl compounds are therefore useful in the treatment of certain psychic and neurologic disorders.

10

Background of the Invention.

A few aminomethylindans and related compounds are known from the prior art.

- 15 So, EP patent 0 281 261 discloses 1-aminomethylindan, 3-aminomethylbenzofurane and 3-aminomethylbenzothiophene derivatives with a hydroxy group or a substituted hydroxy group in the 6-position (indan) or 5-position (benzofurane, benzothiophene). These compounds were found to show central dopamine agonist activity, in particular to show effect at presynaptic dopamine receptors.

20

GB Patent No 2 093 837 A relates to a class of 1-aminoalkyl tetraline derivatives having one or more hydroxy or alkoxy substituents in the 5-, 6- and/or 7-position and claimed to show adrenergic and dopaminergic effects, thus being useful in the treatment of hypertension. DeBernardis et al. in *J. Med. Chem.*, 1985, 28 (10), 1398-
25 1404 discuss such effects with respect to dihydroxy-substituted aminomethyltetralines, -indans and benzocyclobutenes.

- EP Patent No. 0 402 923 A2 discloses 2,5-diaminotetraline derivatives alleged to have central dopamine agonistic activity, with different compounds interacting with
30 different functional dopamine receptors, thus having different therapeutical effects, such as effects in schizophrenia, hypertension and Parkinsonism.

DE Patent No. 39 24 365 A1 describes a class of 2-amino-7-carbamoyltetraline deri-

vatives said to have presynaptic dopamine agonistic properties, and accordingly antihypertensive and heart rate decreasing effects and effects in the central nervous system.

- 5 In U.S. Patent No. 4,500,543 certain 1-aminomethylphtalane compounds are said to show adrenergic effects and, accordingly, antihypertensive and heart rate decreasing properties. Said patent generically covers compounds having substituents in the 5-, 6- and/or 7-position.
- 10 FR Patent No. 2 548 146 relates to 3-aminomethylthiophtalide and 3-aminomethylisobenzofuranethione derivatives claimed to have analgesic and/or anticonvulsive effects.

None of these references discuss or suggest that any of the compounds have 5-HT_{1A} receptor activity.

15

Clinical studies of known compounds having 5-HT_{1A} agonistic activity, such as buspirone, 8-[4-[4-(2-pyrimidyl)-1-piperazinyl]butyl]-8-azaspiro[4,5]decane-7,9-dione, gepirone, 4,4-dimethyl-1-[4-[4-(2-pyrimidyl)-1-piperazinyl]butyl]-2,6-piperidinedione and ipsapirone, 2-[4-[4-(2-pyrimidyl)-1-piperazinyl]butyl]-1,2-benzothiazol-3(2H)-one-1,1-dioxide, have shown that such compounds are useful in the treatment of anxiety disorders such as generalised anxiety disorder, panic disorder, and obsessive compulsive disorder (Glitz, D. A., Pohl, R., *Drugs* 1991, 41, 11). Also preclinical studies indicate that compounds with 5-HT_{1A} agonistic effects are useful in the treatment of the above mentioned anxiety related disorders (Schipper, *Human Psychopharm.*, 1991, 6, S53).

20

25

There is also evidence, both clinical and preclinical, in support of the beneficial effect of compounds having 5-HT_{1A} agonistic activity in the treatment of depression as well as impulse control disorders and alcohol abuse (van Hest, *Psychopharm.*, 1992, 107, 474; Schipper et al, *Human Psychopharm.*, 1991, 6, S53; Cervo et al, *Eur. J. Pharm.*, 1988, 158, 53; Glitz, D. A., Pohl, R., *Drugs* 1991, 41, 11).

30

5-HT_{1A} agonistic compounds inhibits isolation-induced aggression in male mice indicating that these compounds are useful in the treatment of aggression (Sánchez et al, *Psychopharmacology*, 1992, in press).

5 Furthermore, compounds having 5-HT_{1A} agonistic activity have been reported to show antipsychotic effect in animal models (Wadenberg and Ahlenius, *J. Neural Transm.*, 1991, 83, 43; Ahlenius, *Pharm. Tox.*, 1989, 64, 3; Lowe et al., *J. Med. Chem.*, 1991, 34, 1860; New et al., *J. Med. Chem.*, 1989, 32, 1147; and Martin et al., *J. Med. Chem.*, 1989, 32, 1052).

10

Recent studies also indicate that 5-HT_{1A} receptors are important in the serotonergic modulation of haloperidol-induced catalepsy (Hicks, *Life Science* 1990, 47, 1609) suggesting that 5-HT_{1A} agonists are useful in the treatment of the side effects induced by conventional antipsychotic agents such as e.g. haloperidol.

15

Compounds having 5-HT_{1A} agonistic activity have shown neuroprotective properties in rodent models of focal and global cerebral ischaemia and may, therefore, be useful in the treatment of ischaemic disease states (Prehn, *Eur. J. Pharm.* 1991, 203, 213).

20

Both in animal models and in clinical trials it has been shown that 5-HT_{1A} agonists exert antihypertensive effects via a central mechanism (Saxena and Villalón, *Trends Pharm. Sci.* 1990, 11, 95; Gillis et al, *J. Pharm. Exp. Ther.* 1989, 248, 851). Compounds having 5-HT_{1A} agonistic activity may, therefore, be beneficial in the
25 treatment of cardiovascular disorders.

Accordingly, compounds having 5-HT_{1A} agonistic activity are believed to be useful in the therapy of such conditions, and thus being highly desired.

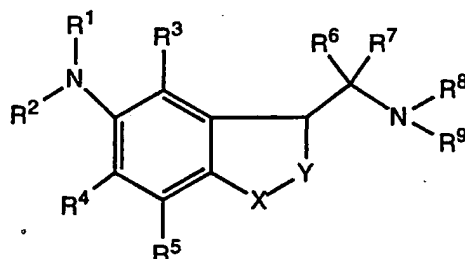
30 Summary of the invention

It has now been found that certain novel aminomethylindans, -2,3-dihydrobenzofuranes, -2,3-dihydrobenzothiophenes, -1,3-dihydroisobenzofuranes and -1,3-dihy-

droisobenzothiophenes have agonistic effect at central 5-HT_{1A} receptors.

Accordingly, the present invention relates to a novel class compounds having general Formula I :

5



I

wherein one of X and Y is CH₂ and the other one is selected from the group consisting of CH₂, O and S;

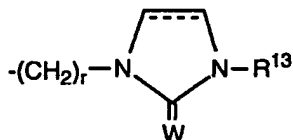
- 10 R¹ is selected from the group consisting of lower alkyl, lower alkenyl, lower alkynyl, cycloalk(en)yl, cycloalk(en)yl-lower alk(en/yn)yl, aryl-lower alkyl, acyl, lower-alkyl sulphonyl, trifluoromethylsulfonyl, arylsulphonyl, R¹⁰ZCO- where Z is O or S and R¹⁰ is alkyl, alkenyl, alkynyl, cycloalk(en)yl, cycloalk(en)ylalkyl, or aryl, or R¹¹R¹²NCO- where R¹¹ and R¹² are independently hydrogen, alkyl, alkenyl, alkynyl, 15 cycloalk(en)yl, cycloalk(en)ylalk(en/yn)yl, or aryl;

R² is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkynyl, cycloalk(en)yl, cycloalk(en)yl-lower alk(en/yn)yl, aryl-lower alkyl;

- R³ - R⁵ are independently selected from the group consisting of hydrogen, halogen, lower alkyl, lower alkoxy, acyl, lower alkylthio, hydroxy, lower alkylsulphonyl, cyano, 20 trifluoromethyl, cycloalkyl, cycloalkylalkyl or nitro;

R⁶ and R⁷ are each hydrogen or lower alkyl or they are linked together to constitute a 3 - 7-membered carbocyclic ring;

R⁸ and R⁹ are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalk(en)yl, cycloalk(en)yl-alk(en/yn)yl, arylalkyl or a group



1a

25

wherein R¹³ is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, cycloalk(en)yl, cycloalk(en)yl-lower alk(en/yn)yl, aryl-lower alkyl or aryl, W is O or S, and r is 2 - 6; or

R⁸ and R⁹ are linked together in order to form a 3 - 7 membered ring containing one nitrogen atom;

any alkyl, cycloalkyl or cycloalkylalkyl group present being optionally substituted with one or two hydroxy groups, which again are optionally esterified with an aliphatic or aromatic carboxylic acid; and any aryl substituent present being optionally substituted with halogen, lower alkyl, lower alkoxy, lower alkylthio, hydroxy, lower alkylsulfonyl, cyano, trifluoromethyl, cycloalkyl, cycloalkylalkyl or nitro; and pharmaceutically acceptable acid addition salts thereof.

10 In general the compounds of the invention have been found potently to inhibit the binding of tritiated 8-hydroxy-2-dipropylaminotetralin (8-OH-DPAT) to 5-HT_{1A} receptors *in vitro*. Furthermore, the present compounds have in general proven to show 5-HT_{1A} agonistic properties *in vivo* and they have been found to show effects in animal models predictive of antipsychotic and anxiolytic properties, respectively.

15 Accordingly, the compounds of the invention are considered useful as drugs for the treatment of psychosis, anxiety disorders, such as generalised anxiety disorder, panic disorder, and obsessive compulsive disorder, depression, impulse control disorders, alcohol abuse, aggression, ischaemic diseases, side effects induced by conventional antipsychotic agents or cardiovascular disorders.

20

Accordingly, in another aspect the invention provides a pharmaceutical composition comprising at least one novel compound according to the invention as defined above or a pharmaceutically acceptable acid addition salt thereof thereof in a therapeutically effective amount and in combination with one or more pharmaceuti-
25 cally acceptable carriers or diluents.

In a further aspect the present invention provides the use of a compound according to the invention or a pharmaceutically acceptable acid addition salt thereof for the manufacture of a pharmaceutical preparation for the treatment of psychosis, anxiety
30 disorders, depression, impulse control disorders, alcohol abuse, aggression, ischaemic diseases, side effects induced by conventional antipsychotic agents or cardiovascular disorders.

Detail d Description of the Invention.

Some of the compounds of general Formula I may exist as optical isomers thereof and such optical isomers are also embraced by the invention.

5

As used herein the term alkyl refers to a C₁-C₂₀ straight chain or branched alkyl group and similarly alkenyl and alkynyl mean a C₂-C₂₀ straight chain or branched hydrocarbon group having one or more double bonds or tripple bonds, respectively.

The term cycloalkyl designates a carbocyclic ring having 3-8 carbon atoms,
10 inclusive, or a bicyclic or tricyclic carbocycle, such as adamantyl.

The terms lower alkyl, lower alkoxy, lower alkylthio, etc. refer to such branched or unbranched groups having from one to six carbon atoms inclusive. Exemplary of such groups are methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl,
15 2-methyl-1-propyl, methoxy, ethoxy, 1-propoxy, methylthio, ethylthio, 1-propylthio, 2-propylthio, methylsulfonyl, ethylsulfonyl, or the like. Similarly lower alkenyl and lower alkynyl refer to such groups having from two to six carbon atoms, inclusive, and one or more double or tripple bonds, respectively.

20 The expression alk(en/yn)yl means that the group may be an alkyl, alkenyl or alkynyl group.

The term aryl refers to a mono- or bicyclic carbocyclic or heterocyclic aromatic group, such as phenyl, indolyl, thienyl, furanyl, pyridyl, thiazolyl, benzofuranyl,
25 benzothienyl, benzisothiazolyl and benzisoxazolyl.

Halogen means fluoro, chloro, bromo or iodo.

As used herein the term acyl refers to a formyl, alkylcarbonyl, alkenylcarbonyl,
30 alkynylcarbonyl, arylcarbonyl, arylalk(en/yn)ylcarbonyl, cycloalkylcarbonyl or cycloalkylalk(en/yn)ylcarbonyl group.

In Formula I, X is preferably CH₂, O or S and Y is CH₂.

R¹ is preferably an aryl-lower alkyl group, an acyl group, a lower alkylsulfonyl group or a group R¹¹R¹²N-CO- wherein R¹¹ is hydrogen or lower alkyl and R¹² is hydrogen, alkyl, aryl, or cycloalkyl. Most preferably, R¹ is benzyl or substituted benzyl, 5 formyl, alkylcarbonyl, in particular acetyl, arylcarbonyl, in particular benzoyl or substituted benzoyl, or a group R¹¹R¹²N-CO- wherein R¹¹ is hydrogen or lower alkyl and R¹² is hydrogen, lower alkyl, phenyl, substituted phenyl, or C₅₋₆ cycloalkyl.

R² is preferably hydrogen or lower alkyl, each of R³, R⁴, R⁵ is preferably hydrogen 10 or halogen and R⁶ and R⁷ are preferably both hydrogen.

R⁸ is preferably hydrogen or lower alkyl, and preferably R⁹ is lower alkyl, aryl-lower alkyl, cycloalkyl-lower alkyl or a group of Formula 1a, wherein W is O and R¹³ is hydrogen, lower alkyl, cycloalkyl or aryl, or alternatively R⁸ and R⁹ are connected 15 in order to form a C₃ - C₇ membered ring containing one nitrogen atom. Most preferably R⁹ is phenyl-lower alkyl, substituted phenyl-lower alkyl, indolyl-lower alkyl, cyclohexyl-lower alkyl or a group of Formula 1a, wherein W is O and R¹³ is hydrogen or a lower alkyl, cycloalkyl, phenyl or substituted phenyl group, or R⁸ and R⁹ are connected in order to form a pyrrolidine or piperidine ring.

20

The acid addition salts of the invention are pharmaceutically acceptable salts of the compounds of Formula I formed with non-toxic acids. Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, embonic, succinic, oxalic, bis-methylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, 25 salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, and theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromotheophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric acids.

30

The pharmaceutical compositions of this invention or those which are manufactured in accordance with this invention may be administered by any suitable route, for example orally in the form of tablets, capsules, powders, syrups, etc., or parente-

rally in the form of solutions for injection. For preparing such compositions methods well known in the art may be used, and any pharmaceutically acceptable carriers, diluents, excipients, or other additive usually used in the art may be used.

- 5 Conveniently, the compounds of the invention are administered in unit dosage form containing said compounds in an amount of about 0.01 to 50 mg.

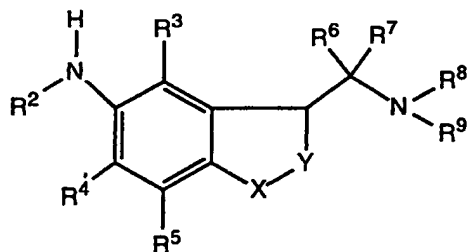
The total daily dose usually ranges of about 0.05 - 500 mg, and most preferably about 0.1 to 20 mg of the active compound of the invention.

10

The invention moreover relates to a method for the preparation of the novel amino-methyl derivatives of indans, 2,3-dihydrobenzofuranes, 2,3-dihydrobenzothiophenes, 1,3-dihydroisobenzofuranes and 1,3-dihydroisobenzothiophenes of Formula I, comprising :

15

- a) acylating an amino derivative of the following Formula II :



II

- 20 wherein R² - R⁹, X, and Y are as previously defined, with an acylating agent such as a carboxylic acid halogenide R^{1'}CO-hal, R^{1'}CO being an acyl group embraced by the definition of R¹ and hal being halogen, a carboxylic acid anhydride or mixed acid anhydride R^{1'}CO-OCOR, R being alkyl, aryl or alkoxy, an isocyanate, isothiocyanate, or a similar activated acylating derivative well-known in the art;

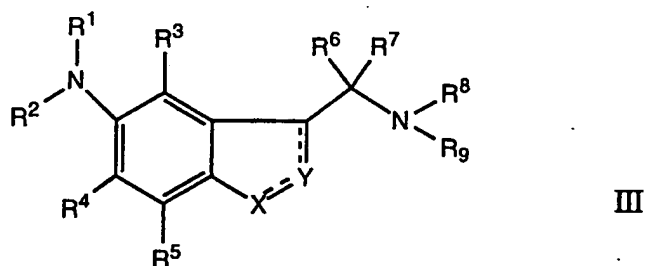
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- b) in order to prepare a compound of Formula I wherein R¹ is lower alkyl, lower alkenyl, lower alkynyl, cycloalk(en)yl, cycloalk(en)yl-lower alk(en/yn)yl or aryl-lower alkyl, alkylating an amino derivative of Formula II with an alkylating agent such as an alkylhalogenide R^{1''}-hal, a mesylate R^{1''}OSO₂CH₃, a tosylate R^{1''}OSO₂C₆H₄-
30 CH₃, or a similar alkylating reagent with suitable leaving groups, R^{1''} being lower

alkyl, lower alkenyl, lower alkynyl, cycloalk(en)yl, cycloalk(en)yl-lower alk(en/yn)yl, or aryl-lower alkyl;

c) reducing the double bond in a compound of the following Formula III :

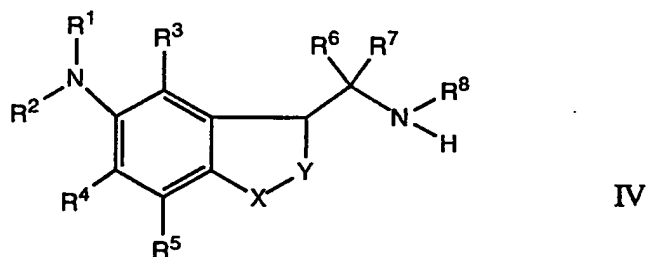
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wherein R¹ - R⁹, X, and Y are as previously defined, at least one of X and Y is CH₂ and one of the two dotted lines indicates a double bond; or

10

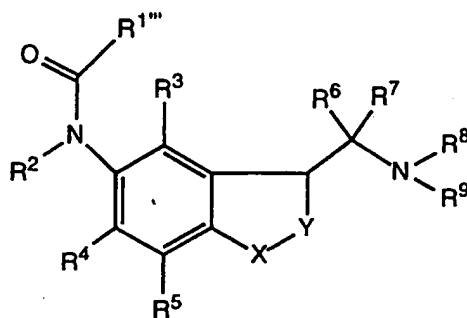
d) alkylating an amine derivative of the following Formula IV :



15 wherein R¹ - R⁸, X, and Y are as previously defined with an alkylating agent such as an alkylhalogenide R⁹-hal, a mesylate R⁹OSO₂CH₃, a tosylate R⁹OSO₂C₆H₄-CH₃, or similar alkylating reagents with suitable leaving groups, wherein R⁹ is as previously defined; or

20 e) in order to prepare a compound of Formula I wherein R¹ is a group as defined previously, however having a methylene group in the 1-position to the amino group, reducing an amide derivative of the following Formula V :

10

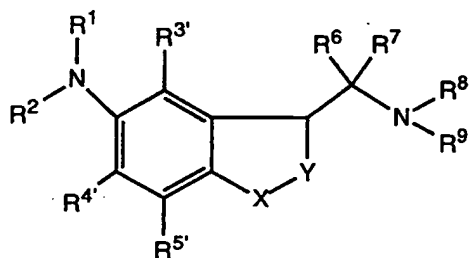


V

wherein R² - R⁹, X and Y are as previously defined and the group R^{1'''}CH₂ constitute a group R¹; or

5

f) introducing a substituent R³, R⁴ or R⁵ by reacting a compound of the following Formula VI :



VI

10

wherein at least one of R^{3'} - R^{5'} is hydrogen and the others are as previously defined for R³, R⁴ or R⁵, and R⁶ - R⁹, X and Y are as previously defined, by using a reactive reagent such as a halogen or a halogenating agent, sulphonating agent, nitration agent, a reactive agent generating carbonium ions (RCO⁺, R⁺) wherein R
15 is alkyl, alkenyl, alkynyl, aryl, cycloalkyl or cycloal(en/yn)yl.

The acylations in Method a) are conveniently performed at low temperatures (eg. below room temperature) in inert solvents such as acetone, dichloromethane, tetrahydrofuran or dimethoxyethane when reactive carboxylic acid chlorides, isocyanates, or isothiocyanates are used. Formylated amines are prepared from the
20 corresponding amines by reaction in formic acid, with esters of formic acid, or by reaction with mixed formic acid anhydride prepared *in situ*. Generally reaction temperatures are between 0 °C and the boiling point of the formyl precursor compounds.

25

Alkylations according to Method b) and d) are generally performed by refluxing in a suitable solvent such as acetone, methyl isobutyl ketone, tetrahydrofuran, dioxane, ethanol or 2-propanol in the presence of a base such as triethylamine or potassium carbonate.

5

Reductions of double bonds according to method c) are generally performed with catalytic hydrogenation at low pressure (< 3 atm.) in a Parr apparatus.

The reductions of the amides according to method e) are generally performed by use of LiAlH_4 , AlH_3 or diborane in an inert solvent, such as diethylether, tetrahydrofuran or dioxane at room temperature or at a slightly elevated temperature. Halogenations according to method f) are generally performed by use of chlorine or bromine or N-chlorosuccinamide, N-bromosuccinimid or another halogen precursor molecule, conveniently in the presence of a catalyst such as Fe ions or a mineral acid.

15

In the following the invention is further illustrated by some examples which, however, may not be construed as limiting.

EXAMPLE 1

20 1-(N,N-dipropylaminomethyl)-6-formylaminoindan, oxalate **1a** (method a)

The starting material, 1-indancarboxylic acid, was prepared according to the procedures of V.Asham and W.H.Linnell, cf. *J.Chem.Soc.* **1954**, 4691-4693. A mixture of indancarboxylic acid (32.2g), thionylchloride (50 ml) and two drops of DMF in dichloromethane (100 ml) was refluxed for 3 hours. Volatile material was evaporated and the remaining crude carboxylic acid chloride was used without further purification. To a solution of N,N-dipropylamine (50 ml) in dichloromethane kept at 0-5 °C was added dropwise a solution of all the crude carboxylic acid chloride in dichloromethane (200 ml). The temperature was gradually raised to room temperature and the reaction mixture was further stirred over-night. The solvents were vaporated *in vacuo* and the remaining viscous oil was purified by filter through silica gel (luted with diethyl ether and dichloromethane 1:1). Yield of N,N-dipropyl-1-indancarboxamide : 32 g. To a well stirred solution of the indan-

carboxamide (20 g) in concentrated H_2SO_4 (120 ml) kept at -10°C was added dropwise a cooled mixture of 100% HNO_3 (6 g) and concentrated H_2SO_4 (40 ml) at -15 to -10°C . The temperature was allowed to raise to 5°C (not higher to avoid formation of the dinitro compound) and the mixture was subsequently poured onto
5 crushed ice (2 kg). Organic material was extracted with diethyl ether (2 x 200 ml), the combined organic phase was washed with diluted aqueous Na_2CO_3 solution (3 x 50 ml). The organic phase was dried (anh. MgSO_4) and treated with activated carbon. Evaporation of diethyl ether *in vacuo* afforded N,N-dipropyl-6-nitro-1-indancarboxamide as an oil (15 g). All of this oil was dissolved in 90% ethanol (250
10 ml). The solution was heated to reflux and Fe powder (10 x 2 g) and 6 M aqueous HCl (10 x 0.2 ml) were added portionwise during 1 hour under vigorous stirring. The mixture was refluxed for another hour. Inorganic material was filtered off while the mixture was still hot. The solution was treated with activated carbon and the solvents subsequently evaporated *in vacuo*. The remaining solid material was
15 recrystallized from a 1:1 mixture of diethyl ether and isopropyl ether yielding 9.5 g of 6-amino-N,N-dipropyl-1-indancarboxamide. Mp: 100°C . To a suspension of LiAlH_4 (4 g) in dry THF was added dropwise a solution of all of the 6-aminoindancarboxamide. The mixture was refluxed for 2 hours and subsequently ice-cooled. A mixture of H_2O /THF was added cautiously to destroy excess of LiAlH_4 . Inorganic
20 salts were filtered off and the filter cake was carefully washed with dichloromethane. The solvents were evaporated *in vacuo*. The remaining oil was dissolved in toluene and excess H_2O was removed by evaporation of toluene leaving the 6-amino-1-(N,N-dipropylaminomethyl)indan as an oil. Yield 7.0 g. To formic acid (98%, 18 ml) was added 3.1 ml of acetic acid anhydride at a temperature just above 0°C . All of
25 the 6-amino-1-(N,N-dipropylaminomethyl)indan was dissolved in dichloromethane (15 ml) and added dropwise at $0-5^\circ\text{C}$. After 1 h stirring at 5°C ethyl acetate (100 ml) and dil. aqueous NH_4OH (100 ml) were added. The organic phase was separated and worked-up as above leaving the title compound 1a as an oil. The oxalate salt crystallized from acetone. Yield 7.4 g. Mp : $150-152^\circ\text{C}$.

30

In a corresponding way the following N,N-disubstituted 6-formylamino-1-amino-methylindans were prepared :

1-(N,N-dimethylaminomethyl)-6-formylaminoindan, oxalate **1b**. Mp: 163-164 °C
6-formylamino-1-(1-piperidinomethyl)indan, fumarate **1c**, Mp : 188-190 °C
6-Formylamino-1-(1-pyrrolidinomethyl)indan, oxalate **1d**. Mp: 176-179 °C.

5 EXAMPLE 2

6-Acetylamino-1-(N,N-dipropylaminomethyl)indan, hydrochloride **2a** (method a).

To a solution of 6-amino-1-(N,N-dipropylaminomethyl)indan (9 g), prepared as in Example 1, in dichloromethane (50 ml) was added triethylamine (4.2 g). A solution
10 of acetylchloride (3.3 g) in dichloromethane (10 ml) was added dropwise at 0-10 °C. The mixture was further stirred at room temperature for 1/2 hour and finally poured into diluted aqueous NH₄OH (100 ml). The organic phase was separated and worked up yielding 11.0 g of crude title product **2a** as an oil. The hydrochloride salt crystallized from acetone. Yield : 9.4 g, mp : 212-216 °C.

15

In a corresponding way the following N,N-disubstituted 6-acylamino-1-aminomethylindans were prepared:

6-Acetylamino-1-(N,N-dimethylaminomethyl)indan, hydrochloride **2b**, Mp: 236-238 °C

20 1-(N,N-dipropylaminomethyl)-6-(4-fluorobenzoylamino)indan, hydrochloride **2c**, Mp: 217-220°C

6-Acetylamino-7-chloro-1-(N,N-dipropylaminomethyl)indan, oxalate **2f**, Mp: 77-79 °C (contains 20 % of 6-amino-7-chloro-1-(N,N-dipropylaminomethyl)indan, dioxalate)

25 1-(N,N-dipropylaminomethyl)-6-(methylsulphonylamino)indan, oxalate **2g**, Mp: >300 °C.

7-chloro-1-(N,N-dipropylaminomethyl)-6-(methylsulphonylamino)indan, oxalate **2h**, Mp: 80-84 °C.

30 5-acetylamino-3-(1-piperidinomethyl)-2,3-dihydrobenzothiophene **2i**, Mp: 126-128 °C

EXAMPLE 3

1-(N,N-dipropylaminomethyl)-6-ureido-indan **3a** (method a)

To a solution of 6-amino-1-(N,N-dipropylaminomethyl)indan (5 g), prepared as in Example 1, in methanol (10 ml) was added acetic acid (7.3 g). A solution of KOCN (3.3 g) in water (5 ml) was added dropwise at 0-10 °C. The mixture was further
5 stirred at room temperature over night. Water (200 ml) and ethylacetate (50 ml) were added and the organic phase was separated and worked up. The fumarate salt of the title compound 3a crystallized from ethanol. The free base was isolated as a crystalline product from the fumarate. Yield 1.1 g. Mp : 101 °C.

10 EXAMPLE 4

1-(N,N-dipropylaminomethyl)-6-(3-phenyl-1-ureido)indan 4a (method a)

To a solution of 6-amino-1-(N,N-dipropylaminomethyl)indan (4.9 g), prepared as in Example 1, in dichloromethane (100 ml) was added phenylisocyanat (3 g). The
15 mixture was refluxed for 1.5 hours. During reaction the title compound 4a crystallized. The mixture was cooled by ice and the precipitated product was filtered off. Yield 4.0 g, mp: 198-201 °C.

In a corresponding way were prepared the following N,N-disubstituted 6-ureido-1-aminomethylindans :
20

1-(N,N-dipropylaminomethyl)-6-(3-methyl-1-ureido)indan, hydrochloride 4b, Mp: 180-182 °C

6-(3,3-dimethyl-1-ureido)-1-(N,N-dipropylaminomethyl)indan; hydrochloride 4c, Mp:
25 185-187 °C

1-(N,N-dipropylaminomethyl)-6-(3-nonyl-1-ureido)indan, hydrochloride 4d, Mp: 148-150 °C

6-(3-cyclopentyl-1-ureido)-1-(N,N-dipropylaminomethyl)indan, 4e, Mp: 136-138 °C

30 EXAMPLE 5

3-(N,N-dipropylaminomethyl)-5-formylamino-2,3-dihydrobenzothiophene, oxalate 5a (method a)

The starting material, 5-amino-2,3-dihydro-N,N-dipropyl-3-benzothiophenecarbox-

amide, was prepared according to the methods in EP Pat. No 88-301073 CA110(9):75302y (1988), *J.Amer.Chem.Soc.* 1948, 70, 1955 and *J.Chem.Soc.(c)* 1967, 1899. To a solution of the carboxamide (10 g) in THF (200 ml) was added LiAlH₄ pellets (3 x 1 g) and the mixture was gently refluxed for 2 h. Excess LiAlH₄ was destroyed by cautiously adding a 10 % solution of water in THF (25 ml) at 20 °C. Inorganic salts were filtered off and the solvents were evaporated *in vacuo*. The remaining oil (7.0 g) was used without further purification. To the thus obtained crude 5-amino-3-(N,N-dipropylaminomethyl)-2,3-dihydrobenzothiophene in toluene (50 ml), 98% formic acid (20 ml) was added. Toluene/formic acid was gradually distilled off until the temperature reached 130-140 °C. Then the mixture was poured onto diluted aqueous NH₄OH (250 ml) and ethyl acetate (100 ml) was added. The organic phase was separated and worked up. The title compound 5a was purified by column chromatography on silica gel (eluted with 3 % triethylamine in a 1:1 mixture of dichloromethane and ethyl acetate). A crystalline oxalate salt was obtained from a 15 % solution of ethanol in acetone. Yield: 2.4 g. Mp: 135-136 °C.

In a corresponding way the following N,N-disubstituted 3-aminomethyl-2,3-dihydrobenzothiophene was prepared:

3-[N-(2-phenylethyl)-N-propylaminomethyl]-5-formylaminomethyl-2,3-dihydrobenzothiophene 5b, isolated as an oil
6-acetylamino-1-(1-piperidinomethyl)indan, oxalate 5c, Mp : 158-160 °C

EXAMPLE 6

1-(N,N-dipropylaminomethyl)-6-(4-fluorobenzylamino)indan, oxalate 6a (method e)

25

To a solution of 6-amino-N,N-dipropyl-1-indancarboxamide (10 g), prepared as in Example 1, and triethylamine (4.2 g) in dichloromethane (75 ml) kept at -5 °C was added dropwise a solution of 4-fluorobenzoylchloride (6 g) in dichloromethane (30 ml). The temperature was slowly raised to roomtemperature. Water (200 ml) was added and the organic phase was worked up leaving 15 g of the crude 4-fluorobenzoylamino derivative as an oil. A small sample was purified and crystallized. Mp: 135 °C. To a suspension of LiAlH₄ (1 g) in dry THF (50 ml) was added the purified 4-fluorobenzoylamino derivative (3 g) and the mixture was gently refluxed for 1

hour. After cooling, excess LiAlH_4 was destroyed by cautiously adding a 10 % solution of water in THF (15 ml) at 20 °C. Inorganic salts were filtered off, the filter cake was thoroughly washed with dichloromethane (2 x 50 ml), and the solvents evaporated leaving the crude title compound 6a as an oil. The oxalate salt (1.5 mol oxalic acid/mol title compound) crystallized from acetone. Yield 1.1 g, mp: 135-140 °C

EXAMPLE 7

5-acetylamino-3-(1-piperidinomethyl)-2,3-dihydrobenzofuran, oxalate 7a (method a)

10 3-Benzofurancarboxylic acid:

To a solution of benzofuran (75 g) in chloroform (600 ml) was added dropwise a solution of bromine (41 ml) in chloroform (150 ml) at -10 °C. The temperature was slowly allowed to reach room temperature and chloroform was evaporated *in vacuo*, leaving the crude 2,3-dibromo-2,3-dihydrobenzofuran as a crystalline product which
15 was used without further purification. Yield : 171 g. To the dibromoderivative (147 g) in ethanol (600 ml) was added a solution of KOH (59 g) in ethanol (200 ml). The mixture was refluxed for 2.5 hours. After cooling to room temperature the mixture was poured onto water and extracted with ethyl acetate (2 x 300 ml). The combined organic phases were worked-up and the 3-bromobenzofuran was subsequently purified
20 by elution through silica gel using n-heptane as the eluent. Yield 51 g of a semicrystalline product. A solution of all of the thus obtained 3-bromobenzofuran and CuCN (33 g) in N-methyl-2-pyrrolidinone (350 ml) was heated at 190 °C under N_2 . With 1 hour intervals was added further CuCN (3 x 4.5g). The mixture was poured into a solution of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ in water (610 ml) and concentrated hydrochloric acid (156
25 ml) while still hot. The resulting mixture was stirred at 60 °C for 1 hour and subsequently poured onto ice/water (5 l). Extraction with diethyl ether (3 x 300 ml) and working-up of the combined organic phases afforded crude, crystalline 3-cyanobenzofuran melting at 76-82 °C. Yield : 34 g. The 3-cyanobenzofuran was dissolved in a mixture of acetic acid:conc. H_2SO_4 :water 1:1:1 (660 ml) and refluxed for 3 hours.
30 After cooling water was added and the 3-benzofurancarboxylic acid was finally extracted with diethyl ether (3 x 200 ml) and worked-up. Yield : 37 g. Mp : 152-156 °C.

3-(1-Piperidylcarbonyl)benzofuran:

A mixture of 3-benzofurancarboxylic acid (15 g), N,N-dimethylformamide (2 ml), and thionyl chloride (25 ml) in dichloromethane (200 ml) was refluxed for 5 hours. Volatile material was evaporated *in vacuo* and excess thionyl chloride was removed by evaporation twice with toluene. The thus obtained 3-benzofurancarboxylic acid chloride was dissolved in dichloromethane (100 ml) and added dropwise to a solution of piperidine (21.4 g) in methylenchloride (100 ml) at 0-5 °C. The mixture was further stirred at room temperature for 1 hour. After washing with water and brine, respectively, the organic phase was worked-up as above. The crude piperidino derivative was further purified by column chromatography on silica gel (eluted with a mixture of ethyl acetate/heptane 3:1) yielding 6.7 g of the pure title compound as an oil.

3-(1-Piperidylcarbonyl)-2,3-dihydrobenzofuran:

To a solution of 3-(1-piperidylcarbonyl)benzofuran (6.7 g) in methanol (150 ml) kept at 35-50 °C were added small portions (in total 3 g) of Mg turnings during 5 hours. After stirring for another hour at 50 °C the mixture was poured onto an aqueous solution of NH₄Cl. The aqueous solution was extracted with dichloromethane (2 x 200 ml). The combined organic phases were worked-up yielding 6.7 g of the title 2,3-dihydrobenzofuran derivative as an oil.

5-Nitro-3-(1-piperidylcarbonyl)-2,3-dihydrobenzofuran:

All of the 2,3-dihydrobenzofuran derivative from above was dissolved in trifluoroacetic acid (35 ml) and cooled to 10 °C. 65 % aqueous HNO₃ 4.3 ml was added dropwise below 10 °C. The solution which had turned black was immediately poured onto ice and extracted with ethyl acetate (2 x 50 ml). The combined organic phases were washed thoroughly with an aqueous Na₂CO₃ solution (2 x 25 ml) and finally with brine. Work-up of the organic phase afforded 6.4 g of crude 5-nitro derivative as an oil. Further purification by column chromatography on silica gel (eluted with ethyl acetate/heptane 3:1) yielded 3.2 g of pure 5-nitro-3-(1-piperidylcarbonyl)-2,3-dihydrobenzofuran which crystallized upon standing. Mp: 108-114 °C.

5-Amino-3-(1-piperidylcarbonyl)-2,3-dihydrobenzofuran:

To a solution of all of the 5-nitrobenzofuran in 90 % ethanol (50 ml) kept at reflux

were added small portions of Fe powder (in total 2.5 g) and concentrated HCl (in total 0.1 ml) during 10 min. The mixture was refluxed for another hour. The inorganic precipitates were filtered off and the mixture was poured onto brine and ethyl acetate (250 ml). work-up of the organic phase afforded 1 g of crystalline 5-aminobenzofuran derivative.

5-Acetylamino-3-(1-piperidinomethyl)-2,3-dihydrobenzofuran, oxalate 7a:

The 5-aminobenzofuran derivative (1 g) dissolved in dry tetrahydrofuran (THF) was added dropwise to a solution of LiAlH_4 (0.5 g) in dry THF (30 ml): The mixture was refluxed for 2 hours. After cooling on an ice bath excess LiAlH_4 was hydrolyzed by addition of aqueous NaOH solution (0.5 ml 15 %). Inorganic salts were filtered off. The THF was evaporated *in vacuo* and the remaining viscous oil was dissolved in dichloromethane (100 ml). After drying (anh. MgSO_4) the dichloromethane was evaporated leaving 0.7 g of crude 5-amino-3-(1-piperidinomethyl)-2,3-dihydrobenzofuran, which was used without further purification. The 5-amino group was acetylated according to the method in EXAMPLE 2. The title compound 7a crystallized as the oxalate salt from acetone. Yield 0.15 g. Mp : 144-150 °C.

EXAMPLE 8

Resolution of compounds

(-)-6-Acetylamino-1-(N,N-dipropylaminomethyl)indan, hydrochloride 8a

To a solution of 6-Acetylamino-1-(N,N-dipropylaminomethyl)indan (36.5 g) prepared as in Example 2, in acetone was added (S)-(+)-binaphthyl-2,2'-diyl hydrogen phosphate ((+)-BNP) (21.2 g) at reflux. The mixture was cooled and left overnight in a refrigerator. The precipitated crystalline product was filtered off and the solution was used for the preparation of the other enantiomer 8b. Recrystallization from a 2:3 mixture of methanol and ethanol afforded 30 g of the (+)-BNP salt. Mp : 257-260 °C. $[\alpha]_D = +293.1^\circ$. The free base of the title compound 8a was isolated ($[\alpha]_D = 84.9^\circ$) and subsequently crystallized as the hydrochloride salt from acetone. Mp : 236-238 °C, $[\alpha]_D = -51.3^\circ$.

(+)-6-Acetylamino-1-(N,N-dipropylaminomethyl)indan, hydrochlorid 8b

The acetone solution from above was poured into water (300 ml) and made alkaline by addition of aqueous diluted NaOH. Extraction with ethyl acetate (2 x 150 ml) and subsequent crystallization of the (-)-BNP salt from acetone/methanol (1:1). Yield: 24.0 g, mp : 257-260 °C, $[\alpha]_D = -296.9^\circ$. The free base was isolated as above ($[\alpha]_D = +84.9^\circ$) and subsequently converted into the hydrochloride salt. Yield : 10.3 g, mp: 236-238 °C, $[\alpha]_D = +54.3^\circ$.

Compound 2b was resolved in a corresponding way using O,O-ditoluyltartaric acid as the resolving agent :

- 10 (-)-6-Acetylamino-1-(N,N-dimethylaminomethyl)indan, isolated as an oil 8c
(+)-6-Acetylamino-1-(N,N-dimethylaminomethyl)indan, isolated as an oil, 8d

Compound 2i was resolved in a corresponding way using O,O-ditoluyltartaric acid as the resolving agent :

- 15 (-)-6-acetylamino-1-(1-piperidinomethyl)indan, (+)-O,O-di(4-toluy)l-D-tartrate 8e, Mp: 144-147 °C. $[\alpha]_D = +59.2$ (The free base was isolated as above ($[\alpha]_D = -46.8^\circ$)
(+)-6-acetylamino-1-(1-piperidinomethyl)indan, (-)-O,O-di(4-toluy)l-L-tartrate 8f, Mp: 141-146 °C. $[\alpha]_D = -56.3^\circ$ (The free base was isolated as above ($[\alpha]_D = +50.7^\circ$)

20 EXAMPLE 9

(-)- and (+)-6-Amino-1-(N,N-dipropylaminomethyl)indan 9a and 9b

Compounds 8a and 8b were hydrolyzed to the corresponding stereoisomers of the 6-aminoindans, respectively :

- 25 A solution of (-)-6-Acetylamino-1-(N,N-dipropylaminomethyl)indan (8.4 g) in 10 % conc. hydrochloric acid in methanol (100 ml) was refluxed for 8 hours. The solvents were evaporated and the remaining oil was added to diluted aqueous NH_4OH (pH > 9) and extracted with ethyl acetate (2 x 100 ml). The organic phase was worked up leaving the (-)-compound 9a as an oil. Yield : 6.5 g, $[\alpha]_D = -81.3^\circ$.

30

In a corresponding way from 8b was prepared :

(+)-6-Amino-1-(N,N-dipropylaminomethyl)indan 9b, $[\alpha]_D = +81.4^\circ$

In a similar way compounds **8c**, **8d**, **9e** and **8f** were hydrolyzed to :

(-)-6-Amino-1-(N,N-dimethylaminomethyl)indan **9c**, isolated as an oil

(+)-6-Amino-1-(N,N-dimethylaminomethyl)indan **9d**, isolated as an oil

(-)-6-amino-1-(1-piperidinomethyl)indan **9e**, isolated as an oil

5 (+)-6-amino-1-(1-piperidinomethyl)indan **9f**, isolated as an oil

EXAMPLE 10

The following resolved derivatives were prepared from compounds **9a** - **9f** using

10 standard acylation procedures as described above :

(-)-1-(N,N-dipropylaminomethyl)-6-formylaminoindan, oxalate **10a**, mp: 149-151 °C,
[α]_D = -44.0°.

(+)-1-(N,N-dipropylaminomethyl)-6-formylaminoindan, oxalate **10b**, mp: 152-154 °C,
[α]_D = +43.9°.

15 (-)-6-(3,3-dimethyl-1-ureido)-1-(N,N-dipropylaminomethyl)indan, hydrochloride **10c**,
mp: 180-182 °C, [α]_D = -49.2°.

(+)-6-(3,3-dimethyl-1-ureido)-1-(N,N-dipropylaminomethyl)indan, hydrochloride **10d**,
mp: 180-182 °C, [α]_D = +48.8°.

(-)-6-[3-(4-fluorophenyl)-1-ureido]-1-(N,N-dipropylaminomethyl)indan, **10e**, mp: 200
20 °C, [α]_D = -68.5°.

(+)-6-[3-(4-fluorophenyl)-1-ureido]-1-(N,N-dipropylaminomethyl)indan, **10f**, mp: 200
°C, [α]_D = +69.8°.

(-)-1-(N,N-dimethylaminomethyl)-6-formylaminoindan, oxalate **10g**, mp: 167-175 °C,
[α]_D = -57.4°.

25 (+)-1-(N,N-dimethylaminomethyl)-6-formylaminoindan, oxalate **10h**, mp: 161-171
°C, [α]_D = +59.5°.

(-)-6-formylamino-1-(1-piperidinomethyl)indan, oxalate **10i**, Mp : 153-160 °C. [α]_D =
-47.3°

(+)-6-Formylamino-1-(1-piperidinomethyl)indan, oxalate **10j**. Mp: 161-164 °C. [α]_D =
30 + 47.4°

EXAMPLE 11

(i) 6-Acetylamino-5-chloro-1-(N,N-dipropylaminomethyl)indan, oxalate **11a**
(method f)

- 5 To a solution of 6-acetylamino-1-(N,N-dipropylaminomethyl)indan **2a** (3.0 g) in acetic acid (15 ml) was added SO_2Cl_2 (1.5 g) in one portion. The temperature raised to 65 °C. After stirring at room temperature for 2 hours the mixture was poured into diluted aqueous NH_4OH and extracted with diethyl ether (2 x 50 ml). The combined organic phases were worked up and the title compound **11a** was purified by column
10 chromatography on silica gel (eluted with ethyl acetate/heptane/triethylamine 40:60:3). The oxalic acid salt crystallized from acetone. Yield: 1.3 g, mp: 172-174 °C.

The enantiomers of **11a** were prepared from the acetyl derivatives **8a** and **8b**, respectively, by chlorination as described above :

- 15 (-)-6-Acetylamino-5-chloro-1-(N,N-dipropylaminomethyl)indan, oxalate **11b**, Mp : 188-194 °C, $[\alpha]_D = -35.4^\circ$.
(+)-6-Acetylamino-5-chloro-1-(N,N-dipropylaminomethyl)indan, oxalate **11c**, Mp : 190-195 °C, $[\alpha]_D = +39.7^\circ$.

- 20 (ii) 6-Acetylamino-5-bromo-1-(N,N-dipropylaminomethyl)indan, oxalate **11d**

To a solution of 6-acetylamino-1-(N,N-dipropylaminomethyl)indan **2a** (5.0 g) in acetic acid (50 ml) was added dropwise a solution of Br_2 (1.2 ml) in acetic acid at 50-55 °C. The mixture was stirred at room temperature overnight. The mixture was
25 poured into water/ethyl acetate, the organic phase was separated and washed with $\text{Na}_2\text{S}_2\text{O}_3$ (1% aqueous solution). After working up of the organic phase, the remaining oil contained a rather high proportion of unreacted starting material and the title compound was isolated from the mixture by column chromatography on silica gel (eluted with ethyl acetate/heptane/triethylamine 40:60:3). The oxalic acid salt of the
30 title compound **11d** crystallized from acetone. Yield : 2.0 g, mp : 156-159 °C.

EXAMPLE 12

6-Acetylamino-1-(N-methylaminomethyl)indan, fumarate **12a** (method g)

To a solution of 6-acetylamino-1-(N,N-dimethylaminomethyl)indan **2b** (54 g) in dioxane (1 L) a solution of 2,2,2-trichloroethyl chloroformate (48.7 g) in dioxane (200 ml) was added dropwise at 50 °C. The mixture was subsequently kept at 50-60 °C for 0.5 h. The solvent was evaporated and the carbamate was purified by filtering through silica (eluted with ethyl acetate). Yield of the crude carbamate as an oil: 89.7 g. To a solution of the thus prepared carbamate (45 g) in 90 % aqueous acetic acid (575 ml) Zn (84 g) was added in small portions at 30-40 °C. After stirring for 3 h excess Zn and Zn salts were filtered off. Water (2 L) was added and extraction with diethyl ether (2 x 200 ml) removed neutral products. The ice cooled H₂O phase was made alkaline (pH >10) by cautiously adding NaOH. Extraction with dichloromethane (4 x 150 ml) and subsequent work-up yielded 14 g of the title compound **12a** as an oil. The fumarate salt crystallized from ethanol. Mp: 176-178 °C.

EXAMPLE 13

6-Acetylamino-1-[N-(4-cyclohexylbutan-1-yl)-N-methylaminomethyl]indan, sesquioxalate **13a** (method d)

A mixture of 6-Acetylamino-1-(N-methylaminomethyl)indan (1.5 g), 4-cyclohexylbutan-1-ol mesylate (2.5 g), potassium carbonate (1.4 g), and a crystal of potassium iodide in MIBK (80 ml) were refluxed for 5 h. After cooling inorganic salts were filtered off and the solvent evaporated *in vacuo*. The remaining oil was subjected to column chromatography on SiO₂ (eluted with ethyl acetate : heptane : triethylamine 80:20:4). The free base of the title compound was isolated as an oil. The sesquioxalate of **13a** crystallized from acetone. Yield 1.6 g Mp: 145-155 °C

In a corresponding way was prepared the following N,N-disubstituted derivatives:

6-Acetylamino-1-[N-methyl-N-(4-phenylbutan-1-yl)aminomethyl]indan, sesquioxalate **13b**. Mp: 121-123 °C.

6-Acetylamino-1-[N-[4-(indol-3-yl)butan-1-yl]-N-methylaminomethyl]indan, oxalate **13 c** Mp: 111-113 °C.

6-Acetylamino-1-[N-[2-(2-imidazolidinon-1-yl)ethyl]-N-methylaminomethyl]indan, sesquioxalate **13d**. Mp: 154-158 °C.

6-Acetylamino-1-[N-[2-[3-(4-fluorophenyl)-2-imidazolidinon-1-yl]ethyl]-N-methylaminomethyl]indan, sesquioxalate **13e**. Mp: 109-114 °C.

6-Acetylamino-1-[N-[4-(3-cyclohexyl-2-imidazolidinon-1-yl)-1-butyl]-N-methylaminomethyl]indan, sesquioxalate **13f**. Mp: 98-101 °C.

5 6-Acetylamino-1-[N-methyl-N-[3-(3-phenyl-2-imidazolidinon-1-yl)-1-propyl]aminomethyl]indan, oxalate **13g**. Mp: 191-194 °C.

6-Acetylamino-1-[N-[4-[3-(4-fluorophenyl)-2-imidazolidinon-1-yl]-1-butyl]-N-methylaminomethyl]indan, oxalate **13h**. Mp: 102-106 °C.

6-Acetylamino-1-[N-[3-(3-cyclohexyl-2-imidazolidinon-1-yl)-1-propyl]-N-methylaminomethyl]indan, sesquioxalate, hemihydrate **13i**. Mp: 108-115 °C.

6-Acetylamino-1-[N-[6-(3-cyclopentyl-2-imidazolidinon-1-yl)-1-hexyl]-N-methylaminomethyl]indan, sesquioxalate, hemihydrate **13j**. Mp: 87-93 °C.

6-Acetylamino-1-[N-[4-(2-imidazolidinon-1-yl)-1-butyl]-N-methylaminomethyl]indan, hemifumarate **13k**. Amorphous freeze dried powder.

15 6-Acetylamino-1-[N-[2-(3-(2-propyl)-2-imidazolidinon-1-yl)ethyl]-N-methylaminomethyl]indan, sesquioxalate, **13l**. Mp: 151-154 °C.

EKSAMPLE 14

6-(N-acetyl-N-ethylamino)-1-(N,N-dipropylaminomethyl)indan, oxalate **14a** (method
20 a)

A solution of the free base of compound **2a** (5.0 g) in dry THF (25 ml) was added dropwise to a suspension of 1 g LiAlH₄ in dry 50 ml THF at 20-25°C. The mixture was refluxed for 2 hours, excess LiAlH₄ was destroyed by cautiously adding 2 ml diluted aqueous NaOH solution. Inorganic salts were filtered off and the crude 6-ethylamino-1-(N,N-dipropylaminomethyl)indan was isolated as a viscous oil upon evaporation of the solvents. Yield : 3.0 g. All of the thus obtained ethylaminoindan derivative was dissolved in 60 ml dichloromethane and 2.3 ml triethylamine was added. The mixture was cooled to 0°C and a solution of 1 ml acetylchloride in 10 ml dichloromethane was added dropwise at 5-10 °C. The mixture was stirred for another hour at room temperature. Water (100 ml) was added and the organic phase was subsequently separated and worked up. The remaining oil was dissolved in acetone and oxalic acid was added. The oxalate salt of the title compound **14a** crystallized

and was filtered off and dried *in vacuo*. Yield: 2.5 g. Mp: 129-130 °C.

The following compound was prepared in a corresponding way using compound 1a as starting material :

- 5 6-(N-acetyl-N-methylamino)-1-(N,N-dipropylaminomethyl)indan, oxalate **14b**, Mp: 126-129 °C.

PHARMACOLOGY

- 10 The compounds of Formula I have been tested according to established and reliable pharmacological methods for determination of the affinity to the 5-HT_{1A} receptor and for determination of the *in vivo* agonistic effects of the compounds with respect to said receptor. The tests were as follows:

- 15 **Inhibition of ³H-8-OH-DPAT Binding to Serotonin 5-HT_{1A} Receptors in Rat Brain *in vitro*.**

By this method the inhibition by drugs of the binding of the 5-HT_{1A} agonist ³H-8-OH-DPAT (1 nM) to 5-HT_{1A} receptors in membranes from rat brain minus cerebellum is determined *in vitro* . Accordingly, this is a test for affinity for the 5-HT_{1A} receptor.

PROCEDURE

Male Wistar (Mol:Wist) rats (125-250 g) are sacrificed and the brain is dissected and weighed. The brain tissue minus cerebellum is homogenized (Ultra Turrax, 20 sec) in 10 ml of ice cold 50 mM Tris buffer pH 8.0 (at 25 °C) containing 120 mM NaCl, 4 mM CaCl₂ and 4 mM MgCl₂. The homogenate is centrifuged at 20,000 g for 10 min at 4 °C. The pellet is homogenized in 10 ml of buffer and incubated at 37 °C for 10 min. The homogenate is centrifuged as above and the pellet is homogenized in 100 vol (w/v) ice cold buffer containing 10 µM of pargyline.

Incubation tubes kept on ice in triplicate receive 100 µl of drug solution in water (or water for total binding) and 1000 µl of tissue suspension (final tissue content corresponds to 10 mg original tissue). The binding experiment is initiated by

- addition of 100 µl of ³H-8-OH-DPAT (final concentration 1 nM) and by placing the tubes in a 37 °C water bath. After incubation for 15 min the samples are filtered under vacuum (0-50 mBar) through Whatman GF/F filters (25 mm). The tubes are rinsed with 5 ml ice cold 0.9% NaCl which is then poured on the filters. Thereafter,
- 5 the filters are washed with 2 x 5 ml 0.9% NaCl. The filters are placed in counting vials and 4 ml of appropriate scintillation fluid (e.g. PicofluorTM15) are added. After shaking for 1 h and storage 2 h in the dark the content of radioactivity is determined by liquid scintillation counting. Specific binding is obtained by subtracting the nonspecific binding in the presence of 10 µM of 5-HT.
- 10 For determination of the inhibition of binding five concentrations of drugs covering 3 decades are used.
- The measured cpm are plotted against drug concentration on semilogarithmic paper, and the best fitting s-shaped curve is drawn. The IC₅₀-value is determined as the concentration, at which the binding is 50% of the total binding in control
- 15 samples minus the nonspecific binding in the presence of 10 µM of 5-HT.
- ³H-8-OH-DPAT was obtained from Amersham International plc., England. Specific activity approximately 200 Ci/mmol.

8-OH DPAT Cue Agonism in Rats

20

This test model is used to determine the agonist effects of a test compound on 5-HT_{1A} receptors *in vivo*. A related method is described by Tricklebank, M. D., *et al*, *Eur. J. Pharmacol.*, 1987, 133, 47-56; Arnt, J. *Pharmacology & Toxicology*, 1989, 64, 165.

25

PROCEDURE

- Male Wistar rats are trained to discriminate between 8-OH-DPAT (0.4 mg/kg, i.p., 15 min pretreatment) and physiological saline in operant chambers equipped with two response levers. Between the levers a dipper is placed, where water rewards
- 30 (0.1 ml) are presented. The rats are water deprived for at least 24 h and work in a fixed ratio (FR) schedule (final FR=32).

Following 8-OH-DPAT administration responding is reinforced only on a designated (drug) lever, whereas responding on the opposite lever has no consequences. Following saline administration responding is reinforced on the lever opposite to the drug lever. Drug and saline trials alternate randomly between days. The level of discrimination accuracy is expressed as the per cent drug responses and is calculated as the number of correct responses x100 divided by the sum of the correct and incorrect responses before the first reward. The time to the first reward is also recorded as a measure of reaction time. When stable accuracy (mean correct responding = 90%; individual rats at least 75% correct responding) is obtained test sessions are included between training days. Test compound is injected s.c. usually 30 min or 45 min, respectively, before beginning of the test. The test trial is terminated when a total of 32 responses are made on either lever or when 20 min have elapsed. No reward is given and the rats have free access to water for 20-30 min after the test. The effects are expressed as per cent drug responding. Only results from rats making at least 10 responses on one lever are included in data analysis. Furthermore, only test sessions in which at least half of the rats respond are included.

The per cent inhibition of drug response obtained for each dose of test compound is used to calculate ED₅₀ values by log-probit analysis.

20

The results obtained will appear from the following Table 1;

The known 5-HT_{1A} receptor ligands 8-OH DPAT and buspirone were included in the tests for comparison purposes.

25

Tabl 1: Pharmacological Test Data

	Compound No.	³ H 8-OH DPAT binding IC ₅₀ nM	8-OH DPAT Cue Agonism ED ₅₀ µM/kg
5			
	1a	4.1	0.0052
	1b	110.	0.41
10	1c	42.	0.33
	1d	19.	
	2a	0.89	0.010
	2b	25.	0.21
	2c	5.1	2.2
15	2f	340.	
	2g	16.	0.93
	2h	2000.	
	2i	6.3	
	3a	0.56	
20	4a	80.	
	4b	6.6	
	4c	10.	0.42
	4d	170.	
	4e	170.	
25	5a	3.4	0.046
	5b	60.	
	5c	6.5	
	6a	20.	
	8a	0.64	0.0089
30	8b	0.64	0.031
	8e	6.7	0.043
	8f	15.	0.15
	10a	1.0	0.010
	10b	4.2	0.058
35	10c	8.1	
	10d	22.	
	10e	160.	
	10f	63.	
	10g	48.	0.12
40	10h	220.	1.9
	11a	21.	0.26
	11b	15.	0.44
	11c	14.	0.38
	11d	120	
45	12a	25.	
	13a	1.4	0.15
	13b	3.4	0.22

Table 1 Cont'd: Pharmacological Test Data

5	Compound No.	³ H 8-OH DPAT binding IC ₅₀ nM	8-OH DPAT Cue Agonism ED ₅₀ μM/kg
	13c	1.5	0.66
	13d	1.8	0.61
10	13e	27.	
	13f	5.1	
	13g	1.0	
	13h	4.8	
	13i	2.2	
15	13j	3.2	
	13k	790.	
	8-OH DPAT	3.5	0.10
	buspirone	41	0.62

20

It appears from the above tables that the compounds of the invention are 5-HT_{1A} receptor ligands inhibiting the binding of tritiated 8-hydroxy-2-dipropylaminotetralin (8-OH-DPAT) to 5-HT_{1A} receptors *in vitro*, many of them with potencies better than 50 nM, and even in the range from about 0.5 to 10 nM. It is also seen that in
25 general they have potent 5-HT_{1A} agonistic properties *in vivo*.

Furthermore, the compounds of the invention were tested with respect to affinity for the dopamine D₂ receptor by determining their ability to inhibit the binding of ³H-spiroperidol to D₂ receptors by the method of Hyttel *et al*, *J. Neurochem.*, **1985**, *44*,
30 1615.

The compounds were also tested in the Methylphenidate test as published by Pedersen and Christensen in *Acta Pharmacol. et Toxicol.* **31**, 488-496 (1972).

35 In a further test, evaluation of catalepsy was made according to the method of Sanchez, C. *et al.*; *Drug Dev. Res.* **1991**, *22*, 239-250.

Th compounds of th invention tested were found to be substantially without affinity to dopamine D₂ receptors and to be without any cataleptogenic eff cts in the

highest dose tested, whereas many of them showed effect in the Methylphenidate Test with ED₅₀ values in the $\mu\text{mol/kg}$ range. These test results indicate that the compounds of the invention have antipsychotic properties without showing extrapyramidal side effects.

5

Finally, the compounds of the invention were tested with respect to anxiolytic properties by measuring their ability to inhibit foot shock-induced ultrasonic vocalisation. Adult rats emit ultrasonic distress calls as response to unavoidable aversive stimuli such as foot shock. This has been suggested as a test model of anxiety
10 (Tonoue T. et al., Psychoneuroendocrinology, 1986, 11, No. 2, 177-184).

The compounds tested showed potent anxiolytic effects in this test with ED₅₀ values generally in the range from 0.03 to 1.0 $\mu\text{mol/kg}$.

15 FORMULATION EXAMPLES

The pharmaceutical formulations of the invention may be prepared by conventional methods in the art.

For example: Tablets may be prepared by mixing the active ingredient with ordinary
20 adjuvants and/or diluents and subsequently compressing the mixture in a conventional tableting machine. Examples of adjuvants or diluents comprise: corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvants or additives usually used for such purposes such as colourings, flavourings, preservatives etc. may be used provided that they are compatible
25 with the active ingredients.

Solutions for injections may be prepared by dissolving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to desired volume, sterilization of the solution and filling in suitable ampules or vials. Any suitable additive conventionally used in the art may
30 be added, such as tonicity agents, preservatives, antioxidants, etc.

Typical examples of recipes for the formulation of the invention are as follows:

- 1) Tablets containing 5.0 mg of Compound 1a calculated as the free base:

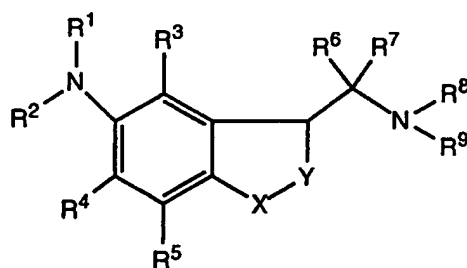
30

	Compound 1a	5.0 mg
	Lactose	60 mg
	Maize starch	30 mg
	Hydroxypropylcellulose	2.4 mg
5	Microcrystalline cellulose	19.2 mg
	Croscarmellose Sodium Type A	2.4 mg
	Magnesium stearate	0.84 mg
2)	Tablets containing 0.5 mg of Compound 2b calculated as the free base:	
10	Compound 2b	0.5 mg
	Lactose	46.9 mg
	Maize starch	23.5 mg
	Povidone	1.8 mg
	Microcrystalline cellulose	14.4 mg
15	Croscarmellose Sodium Type A	1.8 mg
	Magnesium stearate	0.63 mg
3)	Syrup containing per millilitre:	
	Compound 1c	2.5 mg
20	Sorbitol	500 mg
	Hydroxypropylcellulose	15 mg
	Glycerol	50 mg
	Methyl-paraben	1 mg
	Propyl-paraben	0.1 mg
25	Ethanol	0.005 ml
	Flavour	0.05 mg
	Saccharin sodium	0.5 mg
	Water	ad 1 ml
30 4)	Solution for injection containing per millilitre:	
	Compound 10j	0.5 mg
	Sorbitol	5.1 mg
	Acetic acid	0.08 mg
	Water for injection	ad 1 ml

CLAIMS

1. A compound having general Formula I :

5



I

wherein one of X and Y is CH₂ and the other one is selected from the group consisting of CH₂, O and S;

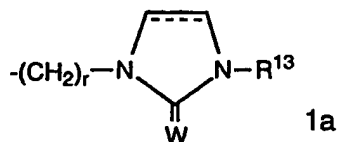
- 10 R¹ is selected from the group consisting of lower alkyl, lower alkenyl, lower alkynyl, cycloalk(en)yl, cycloalk(en)yl-lower alk(en/yn)yl, aryl-lower alkyl, acyl, lower-alkyl sulphonyl, trifluoromethylsulfonyl, arylsulphonyl, R¹⁰ZCO- where Z is O or S and R¹⁰ is alkyl, alkenyl, alkynyl, cycloalk(en)yl, cycloalk(en)ylalkyl, or aryl, or R¹¹R¹²NCO- where R¹¹ and R¹² are independently hydrogen, alkyl, alkenyl, alkynyl, 15 cycloalk(en)yl, cycloalk(en)ylalk(en/yn)yl, or aryl;

R² is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, lower alkynyl, cycloalk(en)yl, cycloalk(en)yl-lower alk(en/yn)yl, aryl-lower alkyl;

- R³ - R⁵ are independently selected from the group consisting of hydrogen, halogen, lower alkyl, lower alkoxy, acyl, lower alkylthio, hydroxy, lower alkylsulpho- 20 nyl, cyano, trifluoromethyl, cycloalkyl, cycloalkylalkyl or nitro;

R⁶ and R⁷ are each hydrogen or lower alkyl or they are linked together to constitute a 3 - 7-membered carbocyclic ring;

R⁸ and R⁹ are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalk(en)yl, cycloalk(en)yl-alk(en/yn)yl, arylalkyl or a group



1a

25

wherein R¹³ is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, cycloalk(en)yl, cycloalk(en)yl-lower alk(en/yn)yl, aryl-lower alkyl or aryl, W is O or S, and r is 2 - 6; or

R⁸ and R⁹ are linked together in order to form a 3 - 7 membered ring containing one nitrogen atom;

any alkyl, cycloalkyl or cycloalkylalkyl group present being optionally substituted with one or two hydroxy groups, which again are optionally esterified with an aliphatic or aromatic carboxylic acid; and any aryl substituent present being optionally substituted with halogen, lower alkyl, lower alkoxy, lower alkylthio, hydroxy, lower alkylsulfonyl, cyano, trifluoromethyl, cycloalkyl, cycloalkylalkyl or nitro; and pharmaceutically acceptable acid addition salts thereof.

10 2. A compound of Claim 1, characterized in that X is CH₂, O or S and Y is CH₂.

3. A compound of Claim 1, characterized in that R¹ is an aryl-lower alkyl group, an acyl group, a lower alkylsulfonyl group or a group R¹¹R¹²N-CO- wherein R¹¹ is hydrogen or lower alkyl and R¹² is hydrogen, alkyl, aryl, or cycloalkyl and R² is hydrogen or lower alkyl..

4. A compound of Claim 3, characterized in that R¹ is benzyl or substituted benzyl, formyl, alkylcarbonyl, arylcarbonyl, or a group R¹¹R¹²N-CO- wherein R¹¹ is hydrogen or lower alkyl and R¹² is hydrogen, lower alkyl, phenyl, substituted phenyl, or C₅₋₆ cycloalkyl.

5. A compound of any of Claims 1 - 4, characterized in that R³, R⁴ and R⁵ are hydrogen or halogen and, R⁶ and R⁷ are both hydrogen .

25 6. A compound of Claim 1, characterized in that R⁸ is hydrogen or lower alkyl, and R⁹ is lower alkyl, aryl-lower alkyl, cycloalkyl-lower alkyl or a group of Formula 1a as defined in Claim 1, in which formula W is O and R¹³ is hydrogen, lower alkyl, cycloalkyl or aryl, or R⁸ and R⁹ are connected in order to form a 3 - 7 membered ring containing one nitrogen atom.

30

7. A compound of Claim 6, characterized in that R⁹ is phenyl-lower alkyl, substituted phenyl-lower alkyl, indolyl-lower alkyl, cyclohexyl-lower alkyl or a group of Formula 1a, wherein W is O and R¹³ is hydrogen or a lower alkyl, cycloalkyl,

phenyl or substituted phenyl group, or R⁸ and R⁹ are connected in order to form a pyrrolidine or piperidine ring.

8. A pharmaceutical composition characterized in that it comprises at least one
5 novel compound of Claim 1 or a pharmaceutically acceptable acid addition salt thereof in a therapeutically effective amount and in combination with one or more pharmaceutically acceptable carriers or diluents.
9. Use of a compound of Claim 1 or a pharmaceutically acceptable acid addition
10 salt thereof for the manufacture of a pharmaceutical preparation for the treatment of psychosis, anxiety disorders, depression, impulse control disorders, alcohol abuse, aggression, ischaemic diseases, side effects induced by conventional antipsychotic agents or cardiovascular disorders.
- 15 10. A method for the treatment of psychosis, anxiety disorders, depression, impulse control disorders, alcohol abuse, aggression, ischaemic diseases, side effects induced by conventional antipsychotic agents or cardiovascular disorders in which a compound of Claim 1 or a pharmaceutically acceptable acid addition salt thereof 1 is administered in a therapeutically effective amount to a person in need
20 thereof.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 93/00413

A. CLASSIFICATION OF SUBJECT MATTER

IPC5: C07C 211/60, C07C 233/15, C07C 233/43, C07C 233/80, C07C 275/40,
C07D 233/36, C07D 307/81, C07D 333/58, C07D 405/06, C07D 409/06
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: C07C, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

REG, CA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 4500543 (JOHN F. DEBERNARDIS ET AL.), 19 February 1985 (19.02.85), see claim 1 --	1
X	WO, A1, 8906645 (ABBOTT LABORATORIES), 27 July 1989 (27.07.89), see claim 1 --	1
A	EP, A2, 0281261 (H. LUNDBECK A/S), 7 Sept 1988 (07.09.88) --	1-9

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

8 March 1994

Date of mailing of the international search report

11-03-1994

Name and mailing address of the ISA/

Swedish Patent Office

Box 5055, S-102 42 STOCKHOLM

Facsimile No. +46 8 666 02 86

Authorized officer

Irja Berlin

Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 93/00413

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>J. Med. Chem., Volume 28, 1985, John F. DeBernardis et al., "Conformationally Defined Adrenergic Agents. 1. Design and Synthesis of Novel α_2 Selective Adrenergic Agents: Electrostatic Repulsion Based Conformational Prototypes" page 1398 - page 1404</p> <p style="text-align: center;">-----</p>	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

28/01/94

International application No.

PCT/DK 93/00413

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US-A-	4500543	19/02/85	NONE		
WO-A1-	8906645	27/07/89	EP-A,B-	0325963	02/08/89
			SE-T3-	0325963	
EP-A2-	0281261	07/09/88	SE-T3-	0281261	
			AU-B-	608293	28/03/91
			AU-A-	1216788	01/09/88
			DE-A-	3870666	11/06/92
			JP-A-	63264557	01/11/88
			US-A-	4847254	11/07/89
			US-A-	4946863	07/08/90